JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

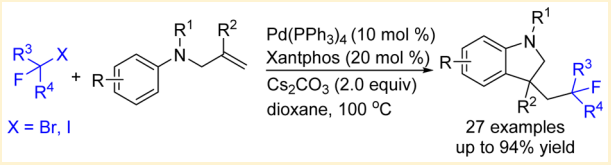
Pd-Catalyzed Arylperfluoroalkylation of Unactivated Olefins for the Synthesis of Heterocycles

Jinhua Zheng, Pan Chen, Yaofeng Yuan,* and Jiajia Cheng*

College of Chemistry, Fuzhou University, 2 Xueyuan Road, Fuzhou 350116, People's Republic of China

Supporting Information

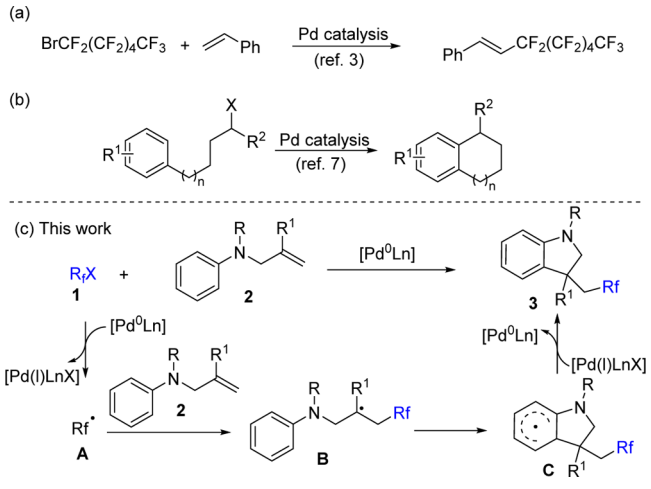
ABSTRACT: An efficient and highly practical palladium-catalyzed arylperfluoroalkylation of unactivated olefins is presented here. A variety of perfluoroalkylated heterocyclic derivatives can be obtained in high regioselectivity. The reaction proceeds mildly without the electronic activation of the aryl group and features high generality, low-cost fluoroalkylated sources and good functional-group compatibility.



INTRODUCTION

The incorporation of fluorinated functional groups into the organic molecules exerts a remarkable effect on their lipophilicity, metabolic stability, and medicinal activities.[1] Therefore, the development of novel methods to prepare fluorinated compounds has become an intensive topic of the synthetic community. The past few years have witnessed the development of Pd-mediated single electron transfer (SET) processes and their increased efficiency for the construction of a carbon−fluorocarbon ($C-R_f$) bond.[2] Perfluoroalkylation of olefins, which are of paramount importance in organic synthesis, has drawn great interest from the chemical society recently. For example, Zhang et al. reported one pioneering study of Pd-catalyzed Heck-type reaction of fluoroalkyl bromides with styrene derivatives in 2015 (Scheme 1a).[3] In this context, the selective difunctionalization of alkenes has received increasing attention, as they enable the incorporation of vicinal functional groups in a single synthetic operation. To date, there have been substantial efforts on Pd-catalyzed perfluoroalkylation of activated alkenes,[4] but difunctionalization of unactivated olefins is less studied[5] due to the side reactions such as deprotonative fluoroalkylation caused by a highly reactive alkyl radical.[6] Recently, Alexanian and co-workers have successfully developed a catalytic C−H alkylation of arenes through the intermediacy of carbon-centered radicals (Scheme 1b).[7] Inspired by the elegant study, we herein disclose the first example of a palladium-catalyzed arylperfluoroalkylation reaction of unactivated olefins. The strategy provides an efficient and general access to a wide range of heterocycles, such as indoline and tetrahydroquinoline, which are also important structural motifs found in numerous pharmaceuticals, agrochemicals, and biologically relevant compounds. This approach utilizes readily available fluoroalkylated sources and features synthetic simplicity, broad substrate scope, and good functional-group compatibility.

Scheme 1. Hypothesis for a Pd-Catalyzed Arylperfluoroalkylation Reaction from Perfluoroalkyl Halides



We envisioned that, under the right set of conditions, a perfluoroalkyl radical **A** could be induced by a palladium complex[8] and is then trapped by an unactivated alkene **2**, with a subsequent intramolecular cyclization leading to the simultaneous formation of carbon−carbon and carbon−fluorocarbon bonds bearing a new quaternary stereocenter (Scheme 1c). However, besides the issue of regioselectivity, a number of potential side reactions[9−11] could complicate the hypothetical reaction. As a result, it is still challenging to realize such a strategy. In contrast, the Pd-catalyzed perfluoroalkylation of unactivated alkenes has been mostly restricted to the formation of iodine atom-transfer compounds.[5a−c] To the best of our knowledge, such a Pd-catalyzed cascade perfluoroalkylation/cyclization reaction of unactivated alkenes has not been reported thus far.

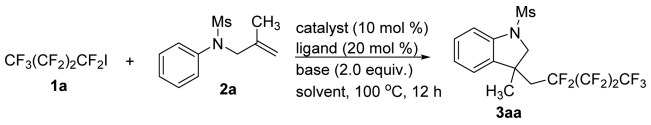
Received: March 15, 2017
Published: May 5, 2017

DOI: 10.1021/acs.joc.7b00598
J. Org. Chem. 2017, 82, 5790−5797

RESULTS AND DISCUSSION

Initially, the arylperfluoalkylation of **2a** was carried out by employing the low-cost and widely available reagent perfluorobutyl iodide **1a** (2.0 equiv) as fluoroalkyl source. Inspired by Zhang's recent report on the palladium-catalyzed difluoroalkylation of organoborons, in which large bite angle bidentate phosphine was used,[8] the reaction was performed with Xantphos[12] as a ligand in the presence of $Pd(OAc)_2$ (10 mol %) and Cs_2CO_3 in dioxane at 100 °C under N_2 atmosphere. To our delight, the expected product **3aa** was isolated in 36% yield after 12 h, and no side products were observed in the process (Table 1, entry 1). After a survey of the prepalladium catalyst,

Table 1. Survey of Reaction Conditions[a,c]



entry	catalyst	ligand	base	solvent	yield (%)[b]
1	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	dioxane	36
2	$Pd(PPh_3)_2Cl_2$	Xantphos	Cs_2CO_3	dioxane	51
3	$Pd(dppf)Cl_2$	Xantphos	Cs_2CO_3	dioxane	76
4	$Pd(MeCN)_2Cl_2$	Xantphos	Cs_2CO_3	dioxane	78
5	$Pd(dba)_2$	Xantphos	Cs_2CO_3	dioxane	75
6	$Pd(PPh_3)_4$	Xantphos	Cs_2CO_3	dioxane	88
7	$Pd(PPh_3)_4$	DPEPhos	Cs_2CO_3	dioxane	43
8	$Pd(PPh_3)_4$	Dppf	Cs_2CO_3	dioxane	29
9	$Pd(PPh_3)_4$	Dppe	Cs_2CO_3	dioxane	<5
10	$Pd(PPh_3)_4$	Binap	Cs_2CO_3	dioxane	<5
11	$Pd(PPh_3)_4$	Xantphos	Na_2CO_3	dioxane	29
12	$Pd(PPh_3)_4$	Xantphos	K_2CO_3	dioxane	33
13	$Pd(PPh_3)_4$	Xantphos	Cs_3PO_4	dioxane	24
14	$Pd(PPh_3)_4$	Xantphos	*t*BuOLi	dioxane	<5
15	$Pd(PPh_3)_4$	Xantphos	Cs_2CO_3	toluene	39
16	$Pd(PPh_3)_4$	Xantphos	Cs_2CO_3	THF	78
17	$Pd(PPh_3)_4$	Xantphos	Cs_2CO_3	DCE	43
18	$Pd(PPh_3)_4$	Xantphos	Cs_2CO_3	DME	37
19[c]	$Pd(PPh_3)_4$	Xantphos	Cs_2CO_3	dioxane	67

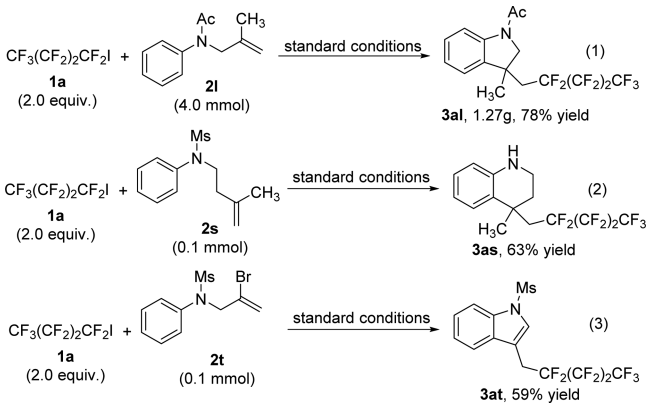
[a]Reaction conditions: perfluorobutyl iodide **1a** (2.0 equiv), **2a** (0.1 mmol), catalyst (10 mol %), ligand (20 mol %), base (2.0 equiv), and solvent (1.0 mL) under N_2 atmosphere at 100 °C for 12 h. [b]Isolated yields. [c]The reaction was stirred at 80 °C for 12 h.

$Pd(PPh_3)_4$ was found to dramatically improve the reaction yield to 88% (Table 1, entries 1−6). In contrast to Xantphos, other bidentate ligands including DPEPhos, Dppe, and BINAP failed to show more catalytic reactivity (Table 1, entries 7−10). A subsequent survey on other reaction parameters indicated that Cs_2CO_3 and dioxane were the most suitable base and solvent (Table 1, entries 11−18). Additionally, the yield decreased to 67% when the reaction temperature dropped to 80 °C (Table 1, entry 19). Finally, the use of **1a** (2.0 equiv), **2a** (1.0 equiv), $Pd(PPh_3)_4$ (10 mol %), Xantphos (20 mol %), and Cs_2CO_3 (2.0 equiv) in dioxane at 100 °C for 12 h was the optimal reaction condition.

Having established optimal reaction conditions (Table 1, entry 6), the substrate scope of the alkenes was evaluated. As depicted in Scheme 2, alkenes with varied electronic properties of the phenyl ring were well tolerated in this protocol, providing high yields of the corresponding perfluoroalkylated indolines in all cases (**3ab**−**3af**). The halogen-substituted substrates (R = Cl or Br) were then tested under the standard conditions, which gave the desired arylperfluoalkylation product (**3ag** or **3ah**) and dehalogenation compound **3aa** as unseparated mixtures. In contrast, iodine-substituted substrate (R = I) showed no desired reaction, and the starting materials were consumed completely. The reaction occurred smoothly when the phenyl group was replaced with a 1-naphthal group (**3ai**). In addition to the mesyl group, substrates bearing other N-protecting groups, regardless of electronic and steric difference, proceeded cleanly to furnish the corresponding products in high yield (**3aj**−**3am**). It is noteworthy that alkene with a sterically encumbered tetrahydroquinoline ring was arylperfluoroalkylated with good yields, thus providing **3an** in high regioselectivity without observation of other side products.

Cursory investigation of diverse perfluoroalkyl iodide with alkenes demonstrated the generality of this catalytic system (Scheme 3). For example, with perfluorooctyl iodide as substrate, alkenes that contain a range of functional groups on the aromatic ring, such as MeO− and CN−, underwent the intended transformation cleanly to give the corresponding products in high yields (**3ba**−**3bd**). In particular, the bulky heptafluoroisopropyl and trifluoromethyl iodide did not interfere with the reaction efficiency, providing **3cl** and **3dd** in good yield. The structure of **3cl** was unambiguously confirmed by an X-ray single-crystal study.[13] Except for perfluoroalkyl iodide, perfluoroalkyl bromide was also tolerated in this transformation (**3ed**). Furthermore, functionalized difluoromethyl iodide/bromide also proved to be a suitable substrate for the present difunctionalization reaction (**3fd**). Gratifyingly, when the methyl group was replaced by H or other alkyl groups (R^2 = H, Bn, $PhCH_2CH_2$), the indoline derivatives (**3ao**−**3aq**) could also be obtained efficiently. Attempts to expand the reaction scope to the substrate containing a phenyl group (R^2 = Ph) or replacing NR^1 to $C(CO_2Et)_2$ failed, as the starting material disappeared and the corresponding transformation did not take place. Finally, it was found that the construction of six-membered rings was also applicable for the reaction, which provided an easy access to the preparation of the polysubstituted tetrahydroquinolines (**3ar**).

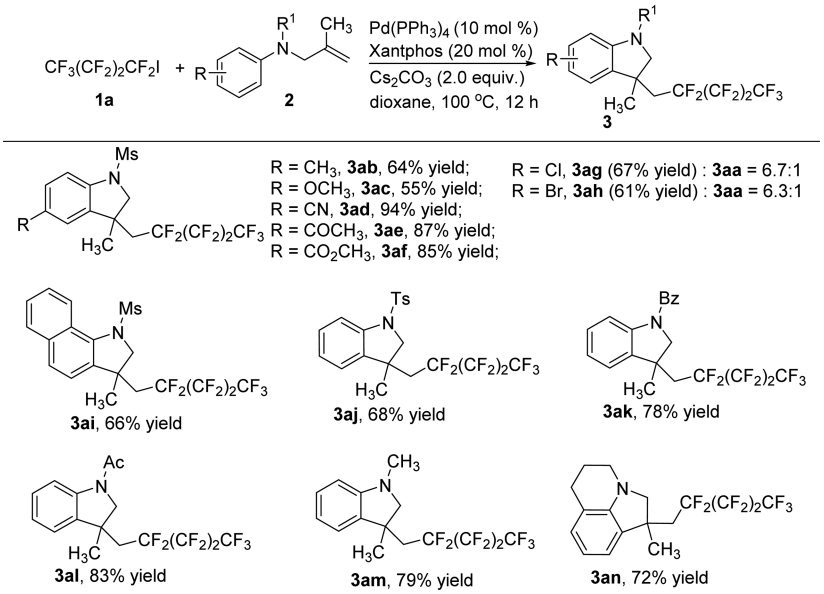
To further demonstrate the practicability of the methodology, a larger-scale reaction of perfluorobutyl iodide **1a** and alkene **2l** was carried out under the optimal conditions. This gave the desired product without any loss of efficiency, as shown by the gram-scale preparation of **3al** (eq 1).



Unexpectedly, we found that the deprotected product **3as** was obtained efficiently in a one-pot procedure, providing a feasible approach for the construction of potentially more bioactive N−H perfluoroalkylated tetrahydroquinoline deriva-

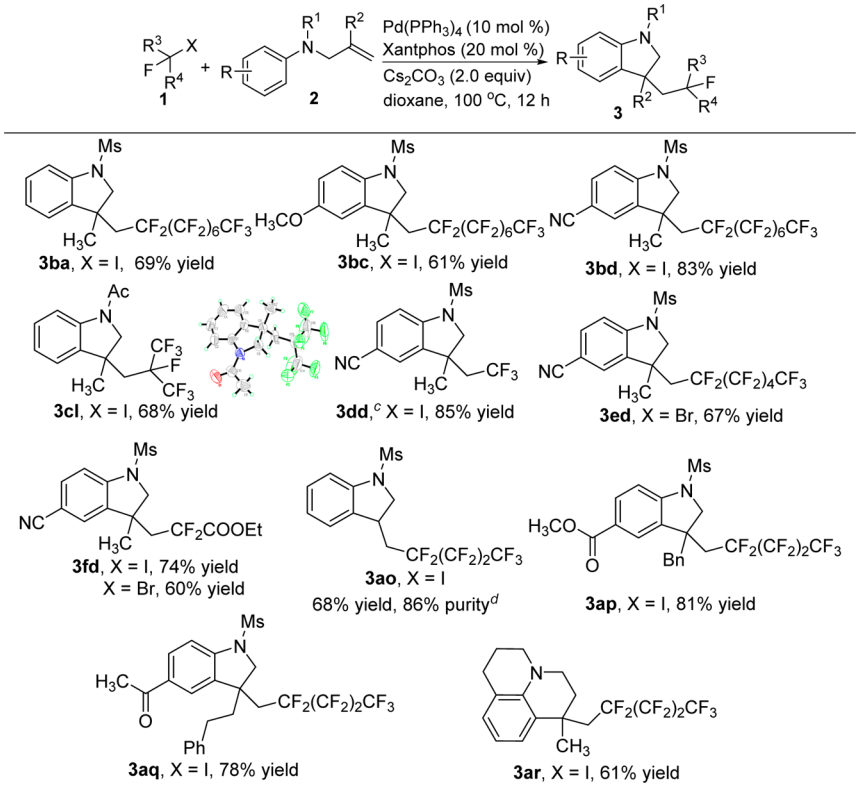
DOI: 10.1021/acs.joc.7b00598
J. Org. Chem. 2017, 82, 5790−5797

Scheme 2. Pd-Catalyzed Arylperfluoroalkylation of Alkenes with 1a[a]



[a](a) Reaction conditions: perfluorobutyl iodide **1a** (2.0 equiv), **2** (0.1 mmol), $Pd(PPh_3)_4$ (10 mol %), Xantphos (20 mol %), and Cs_2CO_3 (2.0 equiv) in anhydrous dioxane (1.0 mL) under N_2 atmosphere at 100 °C for 12 h. (b) Isolated yields.

Scheme 3. Pd-Catalyzed Arylperfluoroalkylation Reaction of Alkenes[a]



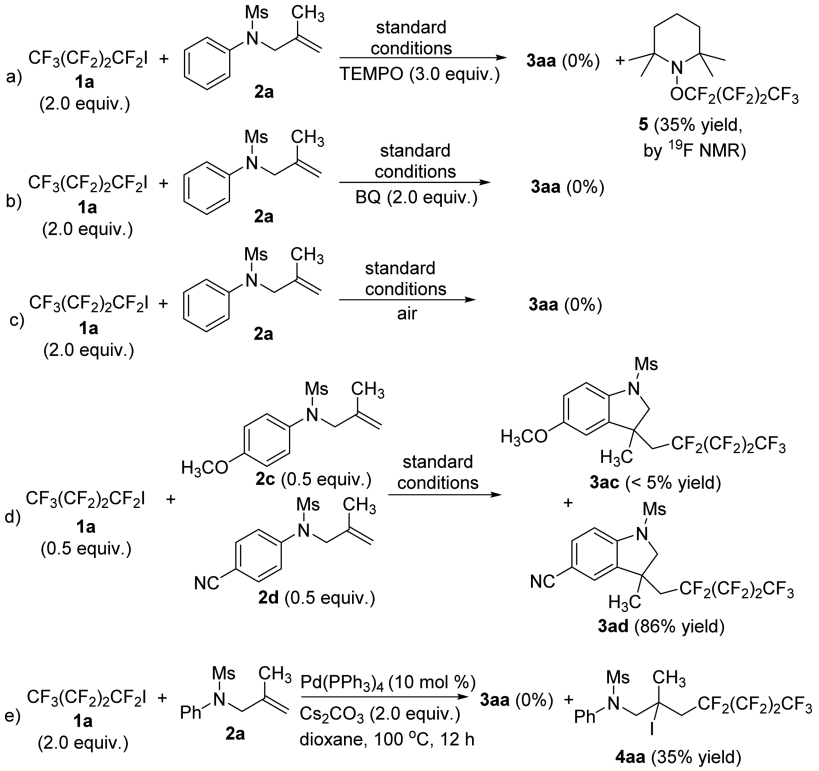
[a](a) Reaction conditions: perfluoroalkyl iodide **1** (2.0 equiv), **2** (0.1 mmol), $Pd(PPh_3)_4$ (10 mol %), Xantphos (20 mol %), and Cs_2CO_3 (2.0 equiv) in anhydrous dioxane (1.0 mL) under N_2 atmosphere at 100 °C for 12 h. (b) Isolated yields. (c) About 4.0 equiv of CF_3I was used and the reaction was stirred at 100 °C for 24 h. (d) The purity was measured by ^{19}F NMR with $PhCF_3$ as an internal standard.

tive (eq 2). When the bromide-substituted substrate **2t** was utilized, only indole derivative **3at** was obtained as the product of the reaction. This result suggested that **3at** may be formed through an arylperfluoroalkylation reaction followed by a base-mediated elimination process (eq 3).

To shed some light into the mechanism, a series of mechanistic studies were designed (Scheme 4). 3.0 equiv of TEMPO (2,2,6,6-tetramethylpiperidinyloxy, radical scavenger)[14] included with the standard conditions substantially suppressed the product formation. Meanwhile, 35% of the

DOI: 10.1021/acs.joc.7b00598
J. Org. Chem. 2017, 82, 5790−5797

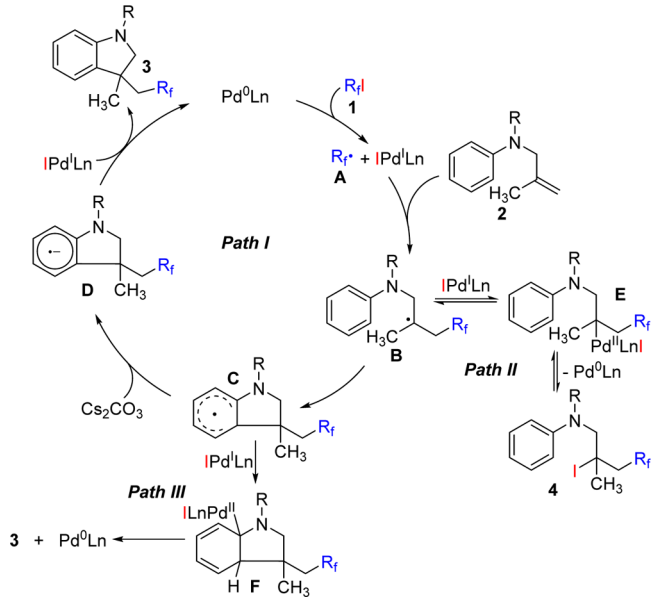
Scheme 4. Mechanistic Studies



TEMPO-C_4F_9 adduct **5** was formed as estimated by ^{19}F NMR spectroscopy (Scheme 4a). Moreover, when the reaction was conducted in the presence of 1,4-benzoquinone (BQ, 2.0 equiv) or air, the substrate **2a** was consumed completely and no product was afforded, implying that a radical intermediate is involved in the catalytic cycle (Scheme 4b and c). We additionally performed one competition reaction between substrate with an electron-donating group **2c** and electron-withdrawing group **2d** (Scheme 4d). In line with a carbon-centered radical species rather than a carbon-cation intermediate, the corresponding product with an electron-withdrawing group **3ad** was furnished as the major product.[15] Finally, the reaction was conducted in the absence of ligand under otherwise identical conditions, and the substrate disappeared without observation of the desired product (Scheme 4e). Instead, 35% yield of iodine atom-transfer product **4aa** was afforded.

On the basis of these results and previous reports,[4,5,7,8] a plausible reaction mechanism was proposed (Scheme 5). The reaction is initiated by a $[Pd^0L_n]$-promoted SET pathway to generate the perfluoroalkyl radical **A** and Pd^IL_nX. The strong electrophilic perfluoroalkyl radicals[16] **A** could attack the electron-rich C−C double bond of **2** to create the carbon-centered radical intermediate **B**. The subsequent addition to the aryl ring would generate the cyclohexadienyl radical **C**, which probably undergoes base-promoted homolytic aromatic substitution (BHAS) mechanism[17] to deliver product **3** and regenerate Pd^0Ln (path I).[18] Alternatively, another pathway can be proposed involving the formation of the corresponding perfluoalkyl iodide **4** as potential reaction intermediates in these transformations (path II).[19] However, we cannot exclude another scenario where Pd^ILnI recombines with **C** to generate palladium complex **F**, which then undergoes β-hydride elimination to deliver the final product (path III).[20]

Scheme 5. Proposed Reaction Mechanism



CONCLUSION

We have developed a palladium-catalyzed arylperfluoroalkylation of unactivated olefins with low-cost and readily available perfluoroalkyl iodides. The approach allowed facile access to a diverse range of valuable perfluoroalkylated heterocyclic products. Varied electronic properties of the aromatic substrates were well tolerated, making this methodology a complementary tool for the existing polar or radical-mediated aromatic ring-forming difunctionalization of olefins. Further investigations to uncover the detailed mechanism and enantioselective modulation are currently underway.

DOI: 10.1021/acs.joc.7b00598
J. Org. Chem. 2017, 82, 5790−5797

EXPERIMENTAL SECTION

General Methods and Materials. Commercially available materials purchased from Alfa Aesar or Aldrich were used as received. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AV400 (400 MHz) spectrometer. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets), m (multiplets), etc. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker AV400 (100 MHz) spectrometer. High-resolution mass spectral analysis (HRMS) was performed on a Waters Q-TOF Premier mass spectrometer. Analytical thin-layer chromatography (TLC) was carried out on Merck 60 F254 precoated silica gel plate (0.2 mm thickness). Visualization was performed using a UV lamp.

Typical Experimental Procedure for the Synthesis of Products 3. To a dry Schlenk tube equipped with a magnetic stir bar were added alkene **2a** (0.1 mmol), $Pd(PPh_3)_4$ (10 mol %), Xantphos (20 mol %), and Cs_2CO_3 (0.2 mmol). The tube was closed with a septum, evacuated, and refilled with nitrogen. Perfluoroalkyl iodide **1a** (0.2 mmol) and freshly distilled dioxane (1 mL) were added, and the reaction mixture was then stirred at 100 °C until **2a** was completely consumed (monitored by TLC). The mixture was concentrated under reduced pressure. The resulting crude residue was purified via column chromatography on silica gel (5:1 hexanes/EtOAc) to afford the desired product **3aa**.

*3-Methyl-1-(methylsulfonyl)-3-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)indoline (**3aa**).* Pale yellow liquid, yield: 39.0 mg (88%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.0 Hz, 1H), 7.26 (t, J = 7.8 Hz, 1H), 7.20 (d, J = 7.2 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 3.98 (d, J = 10.5 Hz, 1H), 3.84 (d, J = 11.9 Hz, 1H), 2.92 (s, 3H), 2.65−2.36 (m, 2H), 1.53 (d, J = 1.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3, 137.5, 129.0, 123.8, 123.0, 113.3, 62.1 (d, J = 5.8 Hz), 41.5, 38.6 (t, J = 20.5 Hz), 34.6, 26.05 (d, J = 3.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −81.30 (t, J = 9.7 Hz, 3F), −108.13 to −113.87 (m, 2F), −124.57 to −124.60 (m, 2F), −125.79 to −125.97 (m, 2F); HRMS (ESI) calcd for $C_{15}H_{14}F_9NNaO_2S$ ($M + Na^+$), 466.0494; found, 466.0473.

*3,5-Dimethyl-1-(methylsulfonyl)-3-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)indoline (**3ab**).* Pale yellow liquid, yield: 29.1 mg (64%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.2 Hz, 1H), 7.07 (d, J = 8.2 Hz, 1H), 6.99 (s, 1H), 3.95 (d, J = 10.5 Hz, 1H), 3.82 (dd, J = 10.6, 1.5 Hz, 1H), 2.90 (s, 3H), 2.62−2.40 (m, 2H), 2.34 (s, 3H), 1.52 (d, J = 2.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 137.7, 133.7, 129.6, 123.5, 113.3, 62.3 (d, J = 6.1 Hz), 41.5, 38.6 (t, J = 20.5 Hz), 34.3, 26.0 (d, J = 3.4 Hz), 20.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −81.20 (t, J = 9.7 Hz, 3F), −108.10 to −113.96 (m, 2F), −124.53 to −124.56 (m, 2F), −125.72 to −125.90 (m, 2F); HRMS (ESI) calcd for $C_{16}H_{16}F_9NNaO_2S$ ($M + Na^+$), 480.0650; found, 480.0637.

*5-Methoxy-3-methyl-1-(methylsulfonyl)-3-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)indoline (**3ac**).* Pale yellow liquid, yield: 26.1 mg (55%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 8.8 Hz, 1H), 6.79 (dd, J = 8.8, 2.5 Hz, 1H), 6.74 (d, J = 2.4 Hz, 1H), 3.96 (d, J = 10.6 Hz, 1H), 3.83−3.80 (m, 4H), 2.89 (s, 3H), 2.55−2.42 (m, 2H), 1.53 (d, J = 1.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 139.2, 133.7, 114.4, 113.6, 109.5, 62.4 (d, J = 5.9 Hz), 55.7, 41.7, 38.4 (t, J = 20.6 Hz), 34.1, 26.0 (d, J = 3.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −81.18 (t, J = 9.6 Hz, 3F), −108.75 to −113.14 (m, 2F), −113.52 to −124.49 (m, 2F), −125.71 to −125.88 (m, 2F); HRMS (ESI) calcd for $C_{16}H_{16}F_9NNaO_3S$ ($M + Na^+$), 496.0599; found, 496.0584.

*3-Methyl-1-(methylsulfonyl)-3-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)indoline-5-carbonitrile (**3ad**).* Pale yellow liquid, yield: 43.9 mg (94%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, J = 8.5, 1.4 Hz, 1H), 7.54−7.46 (m, 2H), 4.09 (d, J = 10.7 Hz, 1H), 3.94 (d, J = 10.5 Hz, 1H), 3.02 (s, 3H), 2.67−2.41 (m, 2H), 1.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 138.4, 133.8, 127.1, 118.5, 113.4, 106.7, 61.94 (d, J = 5.2 Hz), 41.33, 38.4 (t, J = 20.4 Hz), 36.1, 26.5 (d, J = 2.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −81.21 (t, J = 9.7 Hz, 3F), −109.16 to −113.26 (m, 2F), −124.48 to −124.51 (m, 2F), −125.76 to −125.91 (m, 2F); HRMS (ESI) calcd for $C_{16}H_{13}F_9N_2NaO_2S$ ($M + Na^+$), 491.0446; found, 491.0436.

*1-(3-Methyl-1-(methylsulfonyl)-3-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)indolin-5-yl)ethan-1-one (**3ae**).* Pale yellow liquid, yield: 42.2 mg (87%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00−7.75 (m, 2H), 7.47 (d, J = 8.4 Hz, 1H), 4.09 (d, J = 10.6 Hz, 1H), 3.95 (d, J = 10.6 Hz, 1H), 3.02 (s, 3H), 2.79−2.45 (m, 5H), 1.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 144.3, 138.1, 133.0, 130.7, 123.0, 112.3, 62.2, 41.2, 38.5 (t, J = 20.5 Hz), 35.6, 26.4 (d, J = 2.0 Hz), 26.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −81.28 (t, J = 9.6 Hz, 3F), −108.22 to −113.65 (m, 2F), −124.44 to −124.59 (m, 2F), −125.72 to −126.06 (m, 2F); HRMS (ESI) calcd for $C_{17}H_{17}F_9NO_3S$ ($M + H^+$), 486.0780; found, 486.0782.

*Methyl 3-Methyl-1-(methylsulfonyl)-3-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)indoline-5-carboxylate (**3af**).* Pale yellow liquid, yield: 42.9 mg (85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.5 Hz, 1H), 7.88 (s, 1H), 7.45 (d, J = 8.5 Hz, 1H), 4.06 (d, J = 10.6 Hz, 1H), 3.96−3.85 (m, 4H), 3.00 (s, 3H), 2.64−2.47 (m, 2H), 1.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 144.2, 137.7, 131.4, 125.7, 124.6, 112.6, 62.2 (d, J = 6.0 Hz), 52.0, 41.2, 38.7 (t, J = 19.6 Hz), 35.6, 26.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −81.20 (t, J = 9.6 Hz, 3F), −108.29 to −113.85 (m, 2F), −124.33 to −124.53 (m, 2F), −125.68 to −126.00 (m, 2F); HRMS (ESI) calcd for $C_{17}H_{17}F_9NO_4S$ ($M + H^+$), 502.0729; found, 502.0748.

*5-Chloro-3-methyl-1-(methylsulfonyl)-3-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)indoline (**3ag**).* **3ag** and dehalogenation compound **3aa** were obtained as unseparated mixtures (36.3 mg, pale yellow liquid, 67% yield of **3ag**, **3ag**:**3aa** = 6.7:1). **3ag**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J = 8.6 Hz, 1H), 7.23 (dd, J = 8.6, 2.0 Hz, 1H), 7.16 (d, J = 1.9 Hz, 1H), 4.00 (d, J = 10.6 Hz, 1H), 3.86 (d, J = 10.4 Hz, 1H), 2.93 (s, 3H), 2.61−2.41 (m, 2H), 1.54 (d, J = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 139.0, 129.1, 123.5, 114.5, 62.2 (d, J = 5.8 Hz), 41.6, 38.5 (t, J = 20.5 Hz), 34.9, 26.2 (d, J = 3.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −81.19 (t, J = 9.6 Hz, 3F), −107.81 to −113.98 (m, 2F), −124.22 to −124.74 (m, 2F), −125.65 to −126.22 (m, 2F); HRMS (ESI) calcd for $C_{15}H_{14}ClF_9NO_2S$ ($M + H^+$), 478.0285; found, 478.0282.

*5-Bromo-3-methyl-1-(methylsulfonyl)-3-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)indoline (**3ah**).* **3ah** and dehalogenation compound **3aa** were obtained as unseparated mixtures (36.1 mg, pale yellow liquid, 61% yield of **3ah**, **3ah**:**3aa** = 6.3:1). **3ah**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, J = 8.6, 1.8 Hz, 1H), 7.31 (d, J = 8.6 Hz, 1H), 7.28 (d, J = 1.5 Hz, 1H), 3.98 (d, J = 8.0 Hz, 1H), 3.84 (d, J = 10.7 Hz, 1H), 2.93 (s, 3H), 2.70−2.30 (m, 2H), 1.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 139.5, 132.1, 126.3, 116.4, 115.0, 62.2 (d, J = 6.0 Hz), 41.6, 38.6 (t, J = 20.4 Hz), 35.1, 26.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −81.01 (t, J = 9.6 Hz, 3F), −107.94 to −113.68 (m, 2F), −124.34 to −124.64 (m, 2F), −125.54 to −125.76 (m, 2F); HRMS (ESI) calcd for $C_{15}H_{14}BrF_9NO_2S$ ($M + H^+$), 521.9779; found, 521.9773.

*3-Methyl-1-(methylsulfonyl)-3-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-2,3-dihydro-1H-benzo[g]indole (**3ai**).* Pale yellow liquid, yield: 32.5 mg (66%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84−7.70 (m, 2H), 7.63 (d, J = 8.2 Hz, 1H), 7.57−7.39 (m, 3H), 4.28 (d, J = 12.3 Hz, 1H), 3.61 (d, J = 12.3 Hz, 1H), 3.21 (s, 3H), 2.73−2.34 (m, 2H), 1.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 134.5, 134.3, 127.6, 126.1, 125.7, 123.8, 121.9, 121.6, 113.3, 54.5, 38.5, 37.3 (t, J = 17.3 Hz), 30.9, 24.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −81.04 (t, J = 9.6 Hz, 3F), −108.75 to −113.04 (m, 2F), −124.23 to −124.26 (m, 2F), −125.66 to −125.79 (m, 2F); HRMS (ESI) calcd for $C_{19}H_{16}F_9NNaO_2S$ ($M + Na^+$), 516.0650; found, 516.0646.

*3-Methyl-3-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-1-tosylindoline (**3aj**).* Pale yellow liquid, yield: 35.2 mg (68%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75−7.65 (m, 3H), 7.31−7.23 (m, 3H), 7.10−6.98 (m, 2H), 3.92 (d, J = 11.0 Hz, 1H), 3.78 (dd, J = 11.1, 1.2 Hz, 1H), 2.45−2.08 (m, 5H), 1.29 (d, J = 2.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 140.3, 138.0, 133.9, 129.7, 128.9, 127.2, 124.0, 122.8, 114.9, 61.7 (d, J = 6.1 Hz), 41.6, 38.9 (t, J = 20.4 Hz), 26.0 (d, J = 4.6 Hz), 21.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −81.04 (t, J = 9.7 Hz, 3F),

DOI: 10.1021/acs.joc.7b00598
J. Org. Chem. 2017, 82, 5790−5797

−108.51 to −114.19 (m, 2F), −124.50 to −124.53 (m, 2F), −125.28 to −126.44 (m, 2F); HRMS (ESI) calcd for $C_{21}H_{18}F_9NNaO_2S$ (M + Na^+), 542.0807; found, 542.0796.

*(3-Methyl-3-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)indolin-1-yl) (Phenyl)methanone (**3ak**).* Pale yellow liquid, yield: 36.6 mg (78%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, J = 7.7, 1.2 Hz, 1H), 7.56 (td, J = 7.6, 1.4 Hz, 1H), 7.46−7.38 (m, 4H), 7.37−7.32 (m, 2H), 7.31−7.24 (m, 1H), 4.00 (d, J = 12.8 Hz, 1H), 3.87 (d, J = 12.8 Hz, 1H), 2.82−2.31 (m, 2H), 1.66 (d, J = 1.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 144.4, 142.4, 132.8, 129.4, 129.1, 128.2, 127.9, 126.7, 125.3, 124.0, 58.9 (d, J = 3.8 Hz), 36.7 (t, J = 19.7 Hz), 36.5, 22.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −81.11 (t, J = 9.7 Hz, 3F), −110.14 to −113.54 (m, 2F), −124.41 to −124.43 (m, 2F), −125.66 to −125.87 (m, 3F); HRMS (ESI) calcd for $C_{21}H_{17}F_9NO$ [M + H^+], 470.1161; found, 470.1147; calcd for $C_{21}H_{16}F_9NNaO$ (M + Na^+), 492.0980; found, 492.0962.

*1-(3-Methyl-3-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)indolin-1-yl)-ethan-1-one (**3al**).* Pale yellow liquid, yield: 34.0 mg (83%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 8.1 Hz, 1H), 7.30−7.24 (m, 1H), 7.14 (d, J = 7.1 Hz, 1H), 7.09 (t, J = 7.4 Hz, 1H), 4.10 (d, J = 10.8 Hz, 1H), 3.89 (d, J = 10.8 Hz, 1H), 2.58−2.38 (m, 2H), 2.25 (s, 3H), 1.53 (d, J = 1.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 141.1, 137.8, 128.7, 124.0, 121.9, 117.2, 61.24 (d, J = 6.1 Hz), 41.6, 39.2 (t, J = 20.5 Hz), 26.5, 24.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −81.02 (t, J = 9.6 Hz, 3F), −108.62 to −114.17 (m, 2F), −124.48 to −124.50 (m, 2F), −125.58 to −125.78 (m, 3F); HRMS (ESI) calcd for $C_{16}H_{15}F_9NO$ [M + H^+], 408.1004; found, 408.0995; calcd for $C_{16}H_{14}F_9NNaO$ (M + Na^+), 430.0824; found, 430.0813.

*1,3-Dimethyl-3-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)indoline (**3am**).* Pale yellow liquid, yield: 30.0 mg (79%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.13 (t, J = 7.7 Hz, 1H), 7.01 (d, J = 7.3 Hz, 1H), 6.72 (t, J = 7.3 Hz, 1H), 6.52 (d, J = 7.8 Hz, 1H), 3.32 (d, J = 9.2 Hz, 1H), 3.18 (dd, J = 9.2, 2.0 Hz, 1H), 2.75 (s, 3H), 2.53−2.33 (m, 2H), 1.48 (d, J = 2.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 136.9, 128.4, 121.9, 118.2, 107.8, 68.3 (d, J = 5.6 Hz), 41.8, 38.3 (t, J = 20.1 Hz), 35.6, 24.6 (d, J = 3.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −81.18 (t, J = 9.7 Hz, 3F), −108.83 to −113.76 (m, 2F), −124.60 to −124.62 (m, 2F), −125.71 to −125.88 (m, 2F); HRMS (ESI) calcd for $C_{15}H_{15}F_9N$ (M + H^+), 380.1055; found, 380.1045.

*1-Methyl-1-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinoline (**3an**).* Pale yellow liquid, yield: 29.3 mg (72%); ^1H NMR (400 MHz, $CDCl_3$) δ 6.90−6.82 (m, 2H), 6.66 (t, J = 7.4 Hz, 1H), 3.28 (d, J = 8.8 Hz, 1H), 3.15 (dd, J = 8.9, 2.1 Hz, 1H), 3.04−2.90 (m, 2H), 2.69 (t, J = 6.6 Hz, 2H), 2.55−2.27 (m, 2H), 2.13−2.06 (m, 2H), 1.49 (d, J = 2.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 135.2, 127.2, 120.1, 119.5, 118.7, 67.5 (d, J = 5.4 Hz), 46.8, 42.4, 37.9 (t, J = 20.5 Hz), 24.2 (dd, J = 3.7, 1.3 Hz), 23.8, 22.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −81.10 (t, J = 9.7 Hz, 3F), −109.02 to −113.61 (m, 2F), −124.52 to −124.54 (m, 2F), −125.66 to −125.82 (m, 2F); HRMS (ESI) calcd for $C_{17}H_{16}F_9NNa$ (M + Na^+), 428.1031; found, 428.1019.

*3-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,9-Heptadecafluorononyl)-3-methyl-1-(methylsulfonyl)indoline (**3ba**).* White solid, mp 93.8−95.2 °C, yield: 44.5 mg (69%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 8.1 Hz, 1H), 7.27 (t, J = 7.7 Hz, 1H), 7.19 (d, J = 7.3 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 3.98 (d, J = 10.5 Hz, 1H), 3.85 (d, J = 10.3 Hz, 1H), 2.92 (s, 3H), 2.66−2.41 (m, 2H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3, 137.6, 129.1, 123.9, 123.0, 113.4, 62.1 (d, J = 5.7 Hz), 41.6, 38.7 (t, J = 22.3 Hz), 34.6, 26.1 (d, J = 3.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −81.26 (t, J = 9.9 Hz, 3F), −107.98 to −113.65 (m, 2F), −121.41 to −121.81 (m, 2F), −121.90 to −122.42 (m, 4F), −122.81 to −123.32 (m, 2F), −123.46 to −123.89 (m, 2F), −126.28 to −126.68 (m, 2F); HRMS (ESI) calcd for $C_{19}H_{14}F_{17}NNaO_2S$ (M + Na^+), 666.0366; found, 666.0354.

*3-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,9-Heptadecafluorononyl)-5-methoxy-3-methyl-1-(methylsulfonyl)indoline (**3bc**).* White solid, mp 96.5−97.8 ° C, yield: 41.2 mg (61%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 8.7 Hz, 1H), 6.80 (dd, J = 8.8, 2.5 Hz, 1H), 6.76 (d, J = 2.5 Hz, 1H), 3.97 (d, J = 10.4 Hz, 1H), 3.89−3.73 (m, 4H), 2.89 (s, 3H), 2.56−2.54 (m, 2H), 1.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 139.2, 133.7, 114.4, 113.5, 109.5, 62.4, 55.6, 41.8, 38.6 (t, J = 15.1 Hz), 34.0, 25.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −81.28 (t, J = 10.0 Hz, 3F), −107.90 to −113.65 (m, 2F), −121.40 to −121.91 (m, 2F), −122.19 to −122.59 (m, 4F), −122.78 to −123.31 (m, 2F), −123.51 to −124.11 (m, 2F), −126.35 to −126.73 (m, 2F); HRMS (ESI) calcd for $C_{20}H_{16}F_{17}NNaO_3S$ (M + Na^+), 696.0472; found, 696.0462.

*3-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,9-Heptadecafluorononyl)-3-methyl-1-(methylsulfonyl)indoline-5-carbonitrile (**3bd**).* White solid, mp 101.5−102.8 °C, yield: 55.3 mg (83%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.5 Hz, 1H), 7.56−7.48 (m, 2H), 4.10 (d, J = 10.6 Hz, 1H), 3.96 (d, J = 10.6 Hz, 1H), 3.03 (s, 3H), 2.72−2.44 (m, 2H), 1.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 138.5, 133.8, 127.1, 118.5, 113.5, 106.7, 62.0 (d, J = 5.4 Hz), 41.4, 38.5 (t, J = 19.6 Hz), 36.1, 26.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −81.37 (t, J = 8.5 Hz, 3F), −108.37 to −113.13 (m, 2F), −121.45 to −121.91 (m, 2F), −121.98 to −122.48 (m, 4F), −122.92 to 123.32 (m, 2F), −123.56 to −123.92 (m, 2F), −126.38 to −121.72 (m, 2F); HRMS (ESI) calcd for $C_{20}H_{13}F_{17}N_2NaO_2S$ (M + Na^+), 691.0318; found, 691.0315.

*1-(3-Methyl-3-(2,3,3,3-tetrafluoro-2-(trifluoromethyl)propyl)-indolin-1-yl)ethan-1-one (**3cl**).* White solid, mp 121.3−122.5 °C, yield: 24.2 mg (68%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 8.1 Hz, 1H), 7.33−7.24 (m, 1H), 7.15 (d, J = 7.6 Hz, 1H), 7.08 (td, J = 7.5, 0.9 Hz, 1H), 4.09 (d, J = 11.0 Hz, 1H), 3.82 (d, J = 10.0 Hz, 1H), 2.51−2.34 (m, 2H), 2.23 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 141.0, 138.2, 128.8, 124.1, 121.9, 117.3, 60.5, 42.8 (d, J = 2.9 Hz), 36.6 (d, J = 19.7 Hz), 26.5, 24.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.76 to −78.22 (m, 6F), −181.11 to −187.20 (m, 1F); HRMS (ESI) calcd for $C_{15}H_{14}F_7NNaO$ (M + Na^+), 380.0856; found, 380.0842.

*3-Methyl-1-(methylsulfonyl)-3-(2,2,2-trifluoroethyl)indoline-5-carbonitrile (**3dd**).* Pale yellow solid, mp 125.3−126.8 °C, yield: 27.1 mg (85%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.4 Hz, 1H), 7.55−7.37 (m, 2H), 4.10 (d, J = 10.5 Hz, 1H), 3.86 (d, J = 10.6 Hz, 1H), 3.01 (s, 3H), 2.71−2.46 (m, 2H), 1.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 137.9, 133.8, 127.1, 125.6 (q, J = 277.0 Hz), 118.5, 113.3, 106.6, 61.5 (d, J = 1.9 Hz), 42.2 (q, J = 27 Hz), 40.7 (d, J = 1.6 Hz), 36.1, 25.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −60.17 (t, J = 10.9 Hz); HRMS (ESI) calcd for $C_{13}H_{14}F_3N_2O_2S$ (M + H^+), 319.0723; found, 319.0720.

*3-Methyl-1-(methylsulfonyl)-3-(2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoroheptyl)indoline-5-carbonitrile (**3ed**).* Pale yellow liquid, 38.2 mg (67%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.4 Hz, 1H), 7.55−7.37 (m, 2H), 4.07 (d, J = 10.6 Hz, 1H), 3.93 (d, J = 10.6 Hz, 1H), 3.01 (s, 3H), 2.65−2.41 (m, 2H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 138.4, 134.0, 127.1, 118.5, 113.6, 107.0, 62.0, 41.5, 38.7 (t, J = 23.0 Hz), 36.3, 26.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −81.04 (t, J = 9.9 Hz, 3F), −108.49 to −113.21 (m, 2F), −121.58 to −121.96 (m, 2F), −122.61 to −122.21 (m, 2F), −123.48 to −123.78 (m, 2F), −126.00 to −126.69 (m, 2F); HRMS (ESI) calcd for $C_{18}H_{14}F_{13}N_2O_2S$ (M + H^+), 569.0563; found, 569.0562.

*Ethyl 3-(5-Cyano-3-methyl-1-(methylsulfonyl)indolin-3-yl)-2,2-difluoropropanoate (**3fd**).* Pale yellow liquid, yield: X = I, 27.4 mg (74%); X = Br, 22.4 mg (60%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, J = 8.4, 1.3 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.43 (s, 1H), 4.35−4.06 (m, 3H), 3.87 (d, J = 10.6 Hz, 1H), 3.02 (s, 3H), 2.56 (dp, J = 20.9, 15.4 Hz, 2H), 1.50 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3 (t, J = 32.0 Hz), 144.6, 138.1, 133.7, 127.2, 118.5, 115.3 (t, J = 252 Hz), 113.3, 106.4, 63.4, 61.7 (d, J = 2.9 Hz), 42.6 (t, J = 22.0 Hz), 41.2, 36.3, 27.3, 13.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −100.43 (d, J = 131.6 Hz, 1F), −103.09 (d, J = 133.5 Hz, 1F); HRMS (ESI) calcd for $C_{16}H_{18}F_2N_2O_4SNa$ (M + Na^+), 395.0848; found, 395.0843.

*1-(Methylsulfonyl)-3-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)indoline (**3ao**).* Pale yellow liquid, yield: 29.2 mg (68%) (86% purity measured by using $PhCF_3$ as an internal standard); ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.1 Hz, 1H), 7.36−7.28 (m, 1H), 7.22 (d, J = 7.5 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 4.22 (t, J = 9.4 Hz, 1H), 3.77−3.70 (m, 1H), 3.11−2.95 (m, 1H), 2.89 (s, 3H), 2.74−2.55 (m, 1H), 2.48−2.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 132.0, 129.3, 124.4,

DOI: 10.1021/acs.joc.7b00598
J. Org. Chem. 2017, 82, 5790−5797

124.0, 113.7, 56.3, 39.1, 35.39 (t, J = 19.6 Hz), 34.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −81.01 (t, J = 9.3 Hz), −111.92 to −114.31 (m, 2F), −124.22 to −124.45 (m, 2F), −125.75 to −125.96 (m, 2F); HRMS (ESI) calcd for $C_{14}H_{13}F_9NO_2S$ (M + H$^+$), 430.0518; found, 430.0516.

*Methyl 3-Benzyl-1-(methylsulfonyl)-3-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)indoline-5-carboxylate (**3ap**).* Pale yellow liquid, yield: 46.7 mg (81%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.5 Hz, 1H), 7.83 (s, 1H), 7.27 (d, J = 8.5 Hz, 1H), 7.22−7.06 (m, 3H), 6.73 (d, J = 6.6 Hz, 2H), 4.18 (d, J = 11.1 Hz, 1H), 4.04 (d, J = 11.1 Hz, 1H), 3.93 (s, 3H), 3.12 (s, 2H), 2.88−2.54 (m, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 145.4, 135.1, 134.6, 131.8, 130.5, 128.3, 127.3, 125.9, 125.0, 112.0, 58.6 (d, J = 5.8 Hz), 52.1, 45.4, 45.3, 38.4 (t, J = 19.9 Hz), 35.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −81.10 (t, J = 9.6 Hz, 3F), −105.78 to −112.33 (m, 2F), −124.10 to −124.68 (m, 2F), −125.58 to −125.94 (m, 2F); HRMS (ESI) calcd for $C_{23}H_{20}F_9NNaO_4S$ (M + Na$^+$), 600.0862; found, 600.0862.

*1-(1-(Methylsulfonyl)-3-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-3-phenethylindolin-5-yl)ethan-1-one (**3aq**).* Pale yellow liquid, yield: 44.9 mg (78%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99−7.85 (m, 2H), 7.49 (d, J = 8.4 Hz, 1H), 7.25−7.18(m, 2H), 7.18−7.11 (m, 1H), 7.05 (d, J = 7.3 Hz, 2H), 4.16 (d, J = 10.8 Hz, 1H), 4.05 (d, J = 10.9 Hz, 1H), 2.99 (s, 3H), 2.88−2.71 (m, 1H), 2.66−2.51 (m, 5H), 2.45−2.32 (m, 1H), 2.26−2.11 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 145.2, 140.3, 135.2, 132.7, 131.0, 128.4, 128.0, 126.1, 123.8, 112.2, 60.6, 44.7, 41.2, 37.5 (t, J = 20.0 Hz), 35.7, 30.0, 26.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −81.10 (t, J = 9.6 Hz, 3F), −107.68 to −112.61 (m, 2F), −124.20 to −124.43 (m, 2F), −125.55 to −125.80 (m, 2F); HRMS (ESI) calcd for $C_{24}H_{23}F_9NO_3S$ (M + H$^+$), 576.1249; found, 576.1248.

*1-Methyl-1-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-2,3,6,7-tetrahydro-1H,5H-pyrido[3,2,1-ij]quinoline (**3ar**).* Pale yellow liquid, yield: 25.5 mg (61%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, J = 7.7 Hz, 1H), 6.83 (d, J = 7.3 Hz, 1H), 6.55 (t, J = 7.5 Hz, 1H), 3.30−3.00 (m, 4H), 2.76 (t, J = 6.5 Hz, 2H), 2.57−2.11 (m, 3H), 2.11−1.86 (m, 3H), 1.53 (d, J = 2.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 128.6, 127.7, 123.9, 122.0, 115.7, 50.2, 46.1, 39.2 (t, J = 19.7 Hz), 34.8, 33.8 (d, J = 4.4 Hz), 28.4 (d, J = 3.7 Hz), 27.9, 21.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −81.1 (m, J = 9.4 Hz, 3F), −109.83 to −112.59 (m, 2F), −124.11 to −124.41 (m, 2F), −125.59 to −125.70 (m, 2F); HRMS (ESI) calcd for $C_{18}H_{18}F_9NNa$ (M + Na$^+$), 442.1188; found, 442.1174.

*4-Methyl-4-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-1,2,3,4-tetrahydroquinoline (**3as**).* Pale yellow liquid, yield: 23.8 mg (63%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, J = 7.8 Hz, 1H), 7.07−6.94 (m, 1H), 6.65 (t, J = 7.5 Hz, 1H), 6.48 (d, J = 8.0 Hz, 1H), 4.25−3.80 (br, 1H), 3.45−3.22 (m, 2H), 2.63−2.09 (m, 3H), 1.97−1.81 (m, 1H), 1.54 (d, J = 2.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 128.1, 127.5, 126.2, 117.2, 114.6, 39.3 (t, J = 19.8 Hz), 38.0, 34.3, 34.0 (d, J = 3.8 Hz), 28.2 (d, J = 3.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −81.10 (t, J = 9.7 Hz, 3F), −110.38 to −112.55 (m, 2F), −124.45 to −124.48 (m, 2F), −125.64 to −125.74 (m, 2F); HRMS (ESI) calcd for $C_{15}H_{14}F_9NNa$ (M + Na$^+$), 402.0875; found, 402.0864.

*1-(Methylsulfonyl)-3-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-1H-indole (**3at**).* White solid, mp 109.4−110.6 °C, yield: 25.3 mg (59%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.1 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.47 (s, 1H), 7.44−7.32 (m, 2H), 3.52 (t, J = 18.6 Hz, 2H), 3.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.9, 130.5, 126.3, 125.4, 123.8, 119.7, 113.1, 109.9, 40.8, 27.2 (t, J = 23.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −81.06 (t, J = 9.6 Hz), −112.30 to −115.53 (m, 2F), −123.5 to −124.06 (m, 2F), −125.78 to −126.44 (m, 2F); HRMS (ESI) calcd for $C_{14}H_{11}F_9NO_2S$ (M + H$^+$), 428.0361; found, 428.0358.

*Procedure for the Scale-Up Reaction of **3al**.* To a dry Schlenk tube equipped with a magnetic stir bar were added alkene **2l** (4 mmol), $Pd(PPh_3)_4$ (10 mol %), Xantphos (20 mol %), and Cs_2CO_3 (8 mmol). The tube was closed with a septum, evacuated, and refilled with nitrogen. Perfluoroalkyl iodide **1a** (8 mmol) and freshly distilled dioxane (40 mL) were added, and the reaction mixture was then stirred at 100 °C until **2l** was completely consumed (monitored by TLC). The mixture was concentrated under reduced pressure. The resulting crude residue was purified via column chromatography on silica gel (5:1 hexanes/EtOAc) to afford the desired product **3al** (1.27 g, 78% yield).

Radical Inhibition Experiments. To a dry Schlenk tube equipped with a magnetic stir bar were added alkene **2a** (0.1 mmol), $Pd(PPh_3)_4$ (10 mol %), Xantphos (20 mol %), Cs_2CO_3 (0.2 mmol), and TEMPO (0.3 mmol). The tube was closed with a septum, evacuated, and refilled with nitrogen. Perfluoroalkyl iodide **1a** (0.2 mmol) and freshly distilled dioxane (1 mL) were added, and the reaction mixture was then stirred 12 h at 100 °C. The substrate **2a** was completely consumed (monitored by TLC), and the desired product **3aa** was not observed; 35% yield of the TEMPO-C_4F_9 adduct could be detected by ^{19}F NMR (with 0.1 mmol of $PhCF_3$ as a internal standard) of the crude reaction mixture.

To a dry Schlenk tube equipped with a magnetic stir bar were added alkene **2a** (0.1 mmol), $Pd(PPh_3)_4$ (10 mol %), Xantphos (20 mol %), Cs_2CO_3 (0.2 mmol), and benzoquinone (0.2 mmol). The tube was closed with a septum, evacuated, and refilled with nitrogen. Perfluoroalkyl iodide **1a** (0.2 mmol) and freshly distilled dioxane (1 mL) were added, and the reaction mixture was then stirred 12 h at 100 °C. **2a** was completely consumed (monitored by TLC), and the desired product **3aa** was not observed.

To a dry Schlenk tube equipped with a magnetic stir bar were added alkene **2a** (0.1 mmol), $Pd(PPh_3)_4$ (10 mol %), Xantphos (20 mol %), and Cs_2CO_3 (0.2 mmol). Perfluoroalkyl iodide **1a** (0.2 mmol) and freshly distilled dioxane (1 mL) then were added, and the reaction mixture was stirred 12 h at 100 °C. The starting material **2a** was completely consumed (monitored by TLC), and the desired product **3aa** was not observed.

Competition Experiments. To a dry Schlenk tube equipped with a magnetic stir bar were added alkene **2c** (0.05 mmol), alkene **2d** (0.05 mmol), $Pd(PPh_3)_4$ (10 mol %), Xantphos (20 mol %), and Cs_2CO_3 (0.2 mmol). The tube was closed with a septum, evacuated, and refilled with nitrogen. Perfluoroalkyl iodide **1a** (0.05 mmol) and freshly distilled dioxane (1 mL) were added, and the reaction mixture was then stirred at 100 °C for 12 h. The mixture was concentrated under reduced pressure. The resulting crude residue was purified via column chromatography on silica gel (5:1 hexanes/EtOAc) to afford the desired product **3ad** (20.1 mg, 86% yield).

Control Experiments. To a dry Schlenk tube equipped with a magnetic stir bar were added alkene **2a** (0.1 mmol), $Pd(PPh_3)_4$ (10 mol %), and Cs_2CO_3 (0.2 mmol). The tube was closed with a septum, evacuated, and refilled with nitrogen. Perfluoroalkyl iodide **1a** (0.2 mmol) and freshly distilled dioxane (1 mL) were added, and the reaction mixture was then stirred at 100 °C for 12 h. The mixture was concentrated under reduced pressure. The resulting crude residue was purified via column chromatography on silica gel (5:1 hexanes/EtOAc) to afford the iodine atom-transfer product **4aa** (20.1 mg, 35% yield).

*N-(4,4,5,5,6,6,7,7,7-Nonafluoro-2-iodo-2-methylheptyl)-N-phenyl Ethanesulfonamide (**4aa**).* Pale yellow liquid, yield: 20.0 mg (35%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.15 (m, 2H), 6.72 (t, J = 7.3 Hz, 1H), 6.56 (d, J = 7.9 Hz, 2H), 3.63−3.44 (m, 2H), 3.44−3.36 (m, 1H), 3.32−3.18 (m, 2H), 3.09 (t, J = 9.9 Hz, 1H), 2.92−2.72 (m, 2H), 2.44−2.25 (m, 1H), 2.25−2.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 129.3, 116.5, 111.6, 53.1, 51.5 (d, J = 3.3 Hz), 44.7, 34.7, 29.0 (t, J = 22.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −81.00 (t, J = 9.5 Hz, 3F), −112.25 to −115.52 (m, 2F), −123.92 to −124.42 (m, 2F), −125.71 to −126.18 (m, 2F); HRMS (ESI) calcd for $C_{15}H_{16}F_9INO_2S$ (M + H$^+$), 571.9797; found, 571.9793.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00598.

^{1}H, ^{13}C, and ^{19}F NMR spectra of the products (PDF)

X-ray crystallographic data for **3cl** (CIF)

DOI: 10.1021/acs.joc.7b00598
J. Org. Chem. 2017, 82, 5790−5797

AUTHOR INFORMATION

Corresponding Authors

*E-mail: jjcheng@fzu.edu.cn.

*E-mail: yaofeng_yuan@fzu.edu.cn.

ORCID

Jiajia Cheng: 0000-0002-0878-7069

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We gratefully acknowledge the National Natural Science Foundation of China (21502019, 21402027, 21372043), SRF for ROCS, SEM, the Science Foundation of the Fujian Province, China (2015J05021, 2015J05046, 2015H6010), the Education Foundation of Fujian Province, China (JA15095), and Fuzhou University (2016T012) for financial support.

REFERENCES

(1) (a) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 214. (b) Muller, C. K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (d) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308. (e) Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529.

(2) For reviews, see: (a) Liu, Q.; Dong, X.; Li, J.; Xiao, J.; Dong, Y.; Liu, H. *ACS Catal.* **2015**, *5*, 6111. (b) Tang, S.; Liu, K.; Liu, C.; Lei, A. *Chem. Soc. Rev.* **2015**, *44*, 1070. (c) Jahn, U. *Top. Curr. Chem.* **2012**, *320*, 363.

(3) Feng, Z.; Min, Q.-Q.; Zhao, H.-Y.; Gu, J.-W.; Zhang, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 1270.

(4) For recent examples, see: (a) Wang, J.-Y.; Su, Y.-M.; Yin, F.; Bao, Y.; Zhang, X.; Xu, Y.-M.; Wang, X.-S. *Chem. Commun.* **2014**, *50*, 4108. (b) Wang, H.; Guo, L.−N.; Duan, X.-H. *J. Org. Chem.* **2016**, *81*, 860. and references cited therein. For selected examples on the perfluoroalkylation of activated alkenes by using different catalyst/perfluoroalkylating reagents, see: (c) Yang, F.; Klumphu, P.; Liang, Y.-M.; Lipshutz, B. H. *Chem. Commun.* **2014**, *50*, 936. (d) Xu, P.; Xie, J.; Xue, Q.; Pan, C.; Cheng, Y.; Zhu, C. *Chem. - Eur. J.* **2013**, *19*, 14039. (e) Li, L.; Deng, M.; Zheng, S.-C.; Xiong, Y.-P.; Tan, B.; Liu, X.-Y. *Org. Lett.* **2014**, *16*, 504.

(5) (a) Yu, L.-Z.; Zhu, Z.-Z.; Hu, X.-B.; Tang, X.-Y.; Shi, M. *Chem. Commun.* **2016**, *52*, 6581. (b) Yang, S.; Xu, Q.; Shi, M. *Chem. - Eur. J.* **2016**, *22*, 10387. (c) Wang, Y.-Q.; He, Y.-T.; Zhang, L.-L.; Wu, X.-X.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2015**, *17*, 4280. For examples on the perfluoroalkylation of unactivated olefins by using different catalyst/perfluoroalkylating reagents, see: (d) Kawamura, S.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2016**, *55*, 8740. (e) Zhang, Z.; Martinez, H.; Dolbier, W. R. *J. Org. Chem.* **2017**, *82*, 2589.

(6) Selected examples on the deprotonative trifluoromethylation: (a) Parsons, A. T.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 9120. (b) Xu, J.; Fu, Y.; Luo, D.-F.; Jiang, Y.-Y.; Xiao, B.; Liu, Z.-J.; Gong, T.-J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 15300. (c) Wang, X.; Ye, Y.; Zhang, S.; Feng, J.; Xu, Y.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 16410. (d) Chu, L.; Qing, F.-L. *Org. Lett.* **2012**, *14*, 2106. (e) Shimizu, R.; Egami, H.; Hamashima, Y.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 4577.

(7) Venning, A. R. O.; Bohan, P. T.; Alexanian, E. J. *J. Am. Chem. Soc.* **2015**, *137*, 3731.

(8) For a pioneering study of palladium-initiated fluoroalkyl radicals from perfluoroalkyl iodides, see: (a) Chen, Q.-Y.; Yang, Z.-Y.; Zhao, C.-X.; Qiu, Z.-M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 563. For recent examples, see: (b) Li, Z.; García-Domínguez, A.; Nevado, C. *J. Am. Chem. Soc.* **2015**, *137*, 11610. (c) Prieto, A.; Melot, R.; Bouyssi, D.; Monteiro, N. *Angew. Chem., Int. Ed.* **2016**, *55*, 1885. (d) Zhao, H.-Y.; Feng, Z.; Luo, Z.; Zhang, X. *Angew. Chem., Int. Ed.* **2016**, *55*, 10401. (e) Feng, Z.; Min, Q.-Q.; Xiao, Y.-L.; Zhang, B.; Zhang, X. *Angew. Chem., Int. Ed.* **2014**, *53*, 1669. (f) Natte, K.; Jagadeesh, R. V.; He, L.; Rabeah, J.; Chen, J.; Taeschler, C.; Ellinger, S.; Zaragoza, F.; Neumann, H.; Brîckner, A.; Beller, M. *Angew. Chem., Int. Ed.* **2016**, *55*, 2782. (g) Nie, X.; Cheng, C.; Zhu, G. *Angew. Chem., Int. Ed.* **2017**, *56*, 1898 and references cited therein..

(9) Selected examples on the palladium-initiated halogen-atom-transfer reactions: (a) Tsuji, J.; Sato, K.; Nagashima, H. *Tetrahedron* **1985**, *41*, 393. (b) Curran, D. P.; Chang, C. *Tetrahedron Lett.* **1990**, *31*, 933. (c) Monks, B. M.; Cook, S. P. *Angew. Chem., Int. Ed.* **2013**, *52*, 14214. For recent examples on the atom-transfer radical addition reactions of perfluoroalkyl halide, see: (d) Nguyen, J. D.; Tucker, J. W.; Konieczynska, M. D.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2011**, *133*, 4160. (e) Xu, T.; Cheung, C. W.; Hu, X. *Angew. Chem., Int. Ed.* **2014**, *53*, 4910. (f) Tang, X. J.; Dolbier, W. R., Jr. *Angew. Chem., Int. Ed.* **2015**, *54*, 4246. (g) Bagal, D. B.; Kachkovskyi, G.; Knorn, M.; Rawner, T.; Bhanage, B. M.; Reiser, O. *Angew. Chem., Int. Ed.* **2015**, *54*, 6999.

(10) (a) Fruchey, E. R.; Monks, B. M.; Patterson, A. M.; Cook, S. P. *Org. Lett.* **2013**, *15*, 4362. (b) Cheng, Y.; Yu, S. *Org. Lett.* **2016**, *18*, 2962. (c) Choi, S.; Kim, Y. J.; Kim, S. M.; Yang, J. W.; Kim, S. W.; Cho, E. J. *Nat. Commun.* **2014**, *5*, 4881. (d) Gansäuer, A.; Shi, L.; Otte, M.; Huth, I.; Rosales, A.; Sancho-Sanz, I.; Padial, N. M.; Oltra, J. E. *Top. Curr. Chem.* **2011**, *320*, 93.

(11) Wang, Y.-F.; Lonca, G. H.; Chiba, S. *Angew. Chem., Int. Ed.* **2014**, *53*, 1067.

(12) (a) Grushin, V. V.; Marshall, W. J. *J. Am. Chem. Soc.* **2006**, *128*, 12644. (b) Bakhmutov, V. I.; Bozoglian, F.; Gómez, K.; González, G.; Grushin, V. V.; Macgregor, S. A.; Martin, E.; Miloserdov, F. M.; Novikov, M. A.; Panetier, J. A.; Romashov, L. V. *Organometallics* **2012**, *31*, 1315.

(13) X-ray diffraction analysis data for **3cl** are available from the CCDC database: CCDC 1536366.

(14) (a) Phapale, V. B.; Buñuel, E.; García-Iglesias, M.; Cárdenas, D. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8790. (b) Albéniz, A. C.; Espinet, P.; López-Fernández, R.; Sen, A. *J. Am. Chem. Soc.* **2002**, *124*, 11278.

(15) (a) Antunes, C. S. A.; Bietti, M.; Ercolani, G.; Lanzalunga, O.; Salamone, M. *J. Org. Chem.* **2005**, *70*, 3884. (b) Bowman, W. R.; Storey, J. M. D. *Chem. Soc. Rev.* **2007**, *36*, 1803.

(16) Dolbier, W. R., Jr. *Chem. Rev.* **1996**, *96*, 1557.

(17) (a) Studer, A.; Curran, D. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 5018. (b) Zhang, B.; Mück-Lichtenfeld, C.; Daniliuc, C. G.; Studer, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 10792. (c) Studer, A.; Curran, D. P. *Nat. Chem.* **2014**, *6*, 765.

(18) Selected recent examples of palladium(0)-catalyzed hybrid organometallic radical processes: (a) Bloome, K. S.; Alexanian, E. J. *J. Am. Chem. Soc.* **2010**, *132*, 12823. (b) Bloome, K. S.; McMahen, R. L.; Alexanian, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 20146. (c) McMahon, C. M.; Alexanian, E. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 5974. (d) Wu, X.; See, J. W. T.; Xu, K.; Hirao, H.; Roger, J.; Hierso, J.-C.; Zhou, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 13573. (e) Xiao, B.; Liu, Z.-J.; Liu, L.; Fu, Y. *J. Am. Chem. Soc.* **2013**, *135*, 616. (f) Fan, J.-H.; Wei, W.-T.; Zhou, M.-B.; Song, R.-J.; Li, J.-H. *Angew. Chem., Int. Ed.* **2014**, *53*, 6650. (g) Manolikakes, G.; Knochel, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 205. (h) Sumino, S.; Fusano, A.; Fukuyama, T.; Ryu, I. *Acc. Chem. Res.* **2014**, *47*, 1563.

(19) To identify if the fluoroalkylated products were generated by an iodine atom-transfer radical addition to an olefin, followed by Pd-catalyzed ring-forming aromatic C−H alkylation with alkyl iodide, the reaction process was monitored by real-time NMR analysis. The result that no iodoperfluoroalkylated product was observed during the reaction strongly disfavors this hypothesis.

(20) Gu, J.-W.; Zhang, X. *Org. Lett.* **2015**, *17*, 5384.

DOI: 10.1021/acs.joc.7b00598
J. Org. Chem. 2017, 82, 5790−5797